REMARKS

Claims 1, 3, 5-7, 13-19 and 21 are pending in this application. No claim has been added, canceled or amended herein. Accordingly, upon consideration of the remarks made herein, claims 1, 3, 5-7, 13-19 and 21 will still be pending and under examination.

35 U.S.C. §103

The Examiner has rejected claims 1, 3, 5-7, 10-19 and 21 (understood to mean pending claims 1, 3, 5-7, 13-19 and 21) as allegedly obvious over the combination of U.S. Patent No. 6,303,141 (US '141), EP 439 430 (EP '430), Yanagisawa et al. and Bracht.

In response, applicants respectfully traverse, and submit that the claimed invention is not obvious over the combined prior art.

The claimed invention relates to a matrix-controlled transdermal therapeutic system comprising

(i) an active-ingredient-impermeable cover layer,

(ii) a self-adhesive matrix layer, or a plurality of matrix layers of which at least the matrix layer exposed while applying the system is self-adhesive, or one or more matrix layer(s) whose surface remote from the cover layer and intended for adhesion at the application side is coated with an adhesive, the matrix layer(s) comprising at least one ACE inhibitor (angiotensin converting enzyme inhibitor) selected from the group consisting of imidapril, fonisopril, moexipril, perindopril, ramipril, spirapril, cilazapril, benazepril and trandolapril, wherein the inhibitor is in the form of a dicarboxylic acid which is derivatised to form a **diester**, and

(iii) a removable protective layer.

The obviousness rejection is improperly applied to claim 1 because, at least in part, the cited references fail to disclose all of the features recited in claim 1. That is, neither US '141 nor BP '430, Yanagisawa et al. or Bracht teaches or suggests the claimed diester derivatives of ACE inhibitors.

Specifically, as repeatedly admitted in previous Office Actions, US '141 does not teach any diester derivatives of ACE inhibitors, let alone diester derivatives of the claimed ACE inhibitors.

Similarly, as repeatedly confirmed in previous Office Actions, EP '430 teaches a transdermal system that has improved flux through the skin achieved by using specific **salt forms** of the drug. Applicants respectfully submit that a person having ordinary skill in the art would conclude from that statement that salt forms of the active agent are the most preferred active ingredient in the transdermal therapeutic system. The presently claimed invention, however, specifies the active-ingredient to be a **diester** derivative and **not** a salt form. It is again noted that salt forms of ACE inhibitors are not encompassed in the claimed system. As a courtesy, applicants enclose exhibits 1 and 2 showing structural formulas of representatives of the claimed diester derivatives of ACE inhibitors (**Exhibit 1**) and of salt forms disclosed in EP '430 (**Exhibit 2**). As is readily apparent from this representation, EP '430 discloses ACE inhibitors in the form of a **dicarboxylic acid salt** but not in the form of a diester derivative. Accordingly, it is maintained that one of ordinary skill in the art would recognize that the EP '430 reference would not be suggestive of the claimed diester derivatives.

As for Yanagisawa et al., the Examiner asserts that this reference teaches that diesters of diacids of ACE inhibitors are more potent than other derivatives. Applicants disagree. Yanagisawa et al. nowhere teach or suggest diesters of ACE inhibitors to be potent inhibitors.

Notably, Yanagisawa et al. merely teach diester derivatives of ACE inhibitors as intermediates for the preparation of the monoethyl ester hydrochlorides 29 a-d, but not as active agents. In fact, Yanagisawa et al. teaches that certain **monoester** monoacid ACE inhibitor derivatives show a large duration of action. Specifically, the activity of the **monoester** hydrochlorides 29 a, b, d is disclosed. (See biological activity and discussion section, for example, page 424, left column, last paragraph.) Consequently, the combination of features recited in claim 1 is neither disclosed nor suggested in the Yanagisawa et al. reference.

With respect to Bracht, nowhere does this reference teach or suggest diesters of ACE inhibitors. In fact, Bracht is silent about diester derivatives of ACE inhibitors, not to mention the specific ACE inhibitor derivatives recited in claim 1 and their significantly improved stability in the patch.

In view of the foregoing, applicants respectfully submit that the combination of features recited in claim 1 is not taught or suggested by the combination of cited references, since none of the cited references teaches or suggests the claimed diester derivatives of ACE inhibitors as active ingredients of a transdermal therapeutic system, not mention the significantly improved stability of such diester ACE inhibitor derivatives in the patch.

Conclusion

For the above reasons, applicants respectfully submit that the claimed invention is non-obviousness over the cited references. Specifically, there would have been no reasonable expectation of success in practicing the instantly claimed invention based upon the teachings of the prior art. Again, the combination of prior art references on which the Examiner relies does not disclose all of the features recited in claim 1, and thus the remaining pending claims.

This application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited.

It is believed that no additional fees or charges are required at this time in connection with the present application. However, if any additional fees or charges are required at this time, they may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
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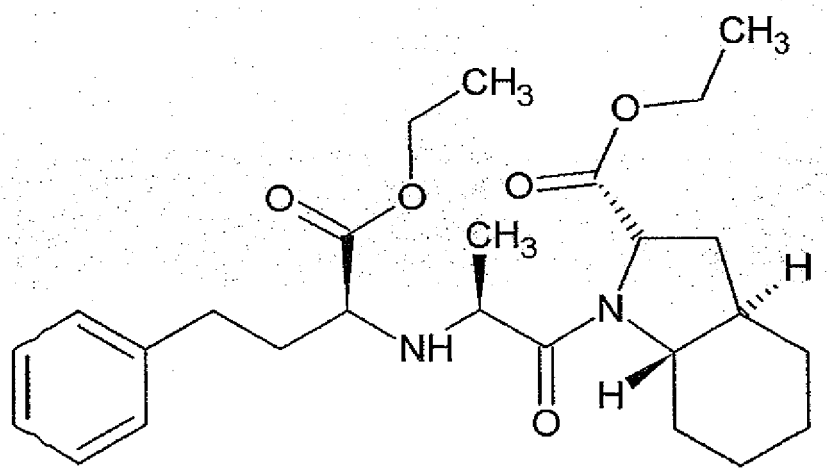
Exhibit 1

Examples of claimed **diester** derivatives of ACE inhibitors.

(1) **Diethyl ester derivative of trandolaprilat (= diacid form of trandolapril)**



(2) **Diethyl ester derivative of benazeprilat**

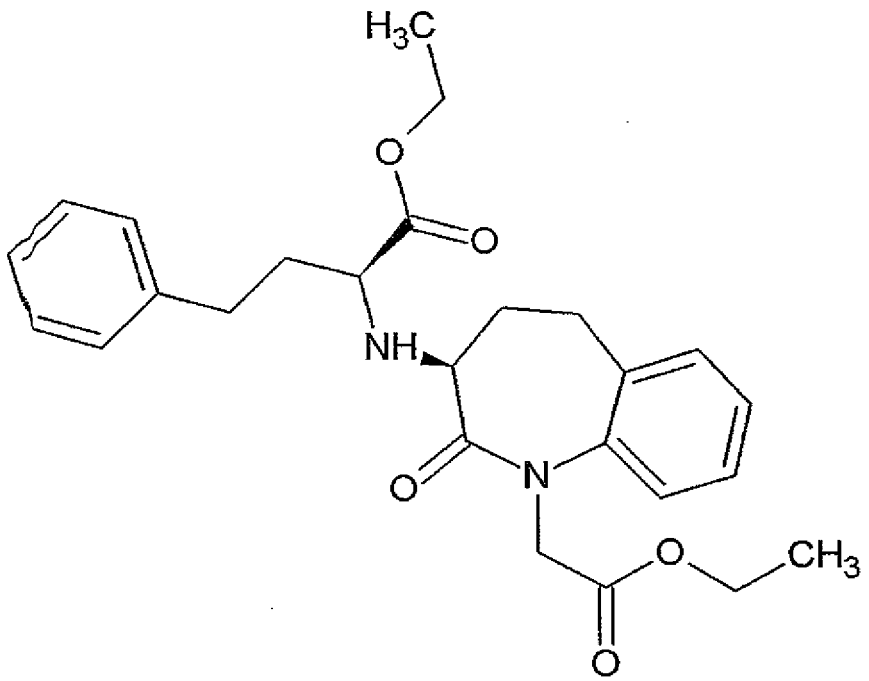
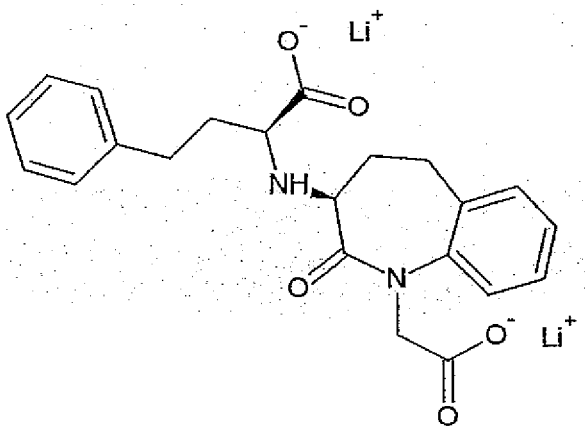


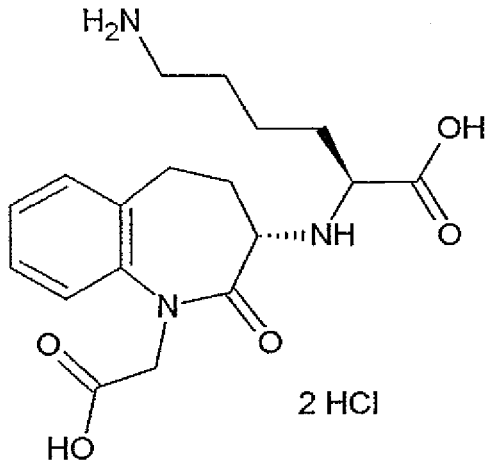
Exhibit 2

Salt forms of ACE inhibitors according to EP '430.

(1) **Benazeprilat dilithium salt**



(2) **Libenzapril dihydrochloride**



(3) **Libenzapril monomaleate**